

PCT 1636

INTERNATIONAL PRELIMINARY EXAMINATION REPORT REC'D 27 JUN 2000

(PCT Article 36 and Rule 70)

WIPO

PCT

Applicant's or agent's file reference 082584/0104		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/07388	International filing date (day/month/year) 14 APRIL 1998	Priority date (day/month/year) 14 APRIL 1997	
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.			
Applicant AMERICAN CYANAMID COMPANY		RECEIVED AUG 03 2000	

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

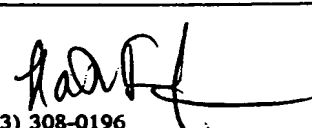
2. This REPORT consists of a total of 4 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 27 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 16 NOVEMBER 1998	Date of completion of this report 30 JUNE 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile N . (703) 305-3230	Authorized officer DAVID GUZO  Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07388

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : Please See Extra Sheet. US CL : Please See Extra Sheet. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/5, 6, 7.1, 29, 69.1, 172.3, 235.1, 320.1, 325, 348, 352, 254.11; 536/23.1, 23.5; 530/350 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, Dialog, Biosis, Medline, Biotech, Biosci Search terms: juvenile hormone, juvenile hormone receptor, basic helix loop helix, methoprene tolerant, insecticides		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YAO et al. Drosophila Ultraspiracle Modulates Ecdysone Receptor Function via Heterodimer Formation. Cell. 02 October 1992, Vol. 71, pages 63-72, especially 69-70.	1-51
A	SHEMSHEDINI et al. Resistance to Juvenile Hormone and an Insect Growth Regulator in Drosophila is Associated with an Altered Cytosolic Juvenile Hormone-Binding Protein. Proceedings of the National Academy of Sciences. March 1990, Vol. 87, pages 2072-2076, especially page 2075.	1-51
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *&* document member of the same patent family	
Date of the actual completion of the international search 20 MAY 1998		Date of mailing of the international search report 06 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer DAVID GUZO <i>[Signature]</i> Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07388

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KELLEY et al. Restriction of P-Element Insertions at the Notch Locus of Drosophila Melanogaster. Molecular and Cellular Biology. April 1987, Vol. 7, No. 4, pages 1545-1548, especially page 1546.	1-51

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/07388

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C12N 1/15, 5/10, 15/11, 15/63, 15/81, 15/86; C07H 21/04; C07K 14/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

435/5, 6, 7.1, 29, 69.1, 172.3, 235.1, 320.1, 325, 348, 352, 254.11; 536/23.1, 23.5; 530/350

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 December 1998 (14.12.98)	
International application No. PCT/US98/07388	Applicant's or agent's file reference 082584/0104
International filing date (day/month/year) 14 April 1998 (14.04.98)	Priority date (day/month/year) 14 April 1997 (14.04.97)
Applicant WILSON, Thomas, G. et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

16 November 1998 (16.11.98)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

- ☐ the international application as originally filed.
- ☒ the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____
pages _____ , filed with the letter of _____
- ☒ the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____
Nos. _____ , filed with the letter of _____
- ☒ the drawings, sheets/fig (See Attached) , as originally filed.
sheets/fig _____ , filed with the demand.
sheets/fig _____ , filed with the letter of _____
sheets/fig _____ , filed with the letter of _____

2. The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/07388

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)

Claims 1-51 YESClaims NONE NO

Inventive Step (IS)

Claims 1-51 YESClaims NONE NO

Industrial Applicability (IA)

Claims 1-51 YESClaims NONE NO**2. CITATIONS AND EXPLANATIONS**

Claims 1-51 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the isolated bHLH-PAS polypeptides, nucleic acid sequences encoding said polypeptides, expression vectors containing said nucleic acids, host cells containing said expression vectors, methods of screening compounds that specifically bind with a bHLH-PAS/JHR polypeptide and methods of detecting JH-resistant individuals in a population. The invention has industrial applicability in that the invention provides for an efficient method for testing insecticides targeted for the JH system in insects.

_____ NEW CITATIONS _____
NONE

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AUG 23 2000

TECH CENTER 1600/2900

Suppl mental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): C12N 1/15, 5/10, 15/11, 15/63, 15/81, 15/86; C07H 21/04; C07K 14/00 and US Cl.: 435/5, 6, 7.1, 29, 69.1, 172.3, 235.1, 320.1, 325, 348, 352, 254.11; 536/23.1, 23.5; 530/350

I. BASIS OF REPORT:This report has been drawn on the basis of the description,
pages, 2, 3, 5-65 and 68-69, as originally filed.

pages, NONE, filed with the demand.

and additional amendments:

Pages 1, 4, 66 and 67, and sequence listing pages 1-22, filed with the letter of 11 May 1999.

This report has been drawn on the basis of the claims,
numbers, 1-35 and 44-51, as originally filed.

numbers, NONE, as amended under Article 19.

numbers, NONE, filed with the demand.

and additional amendments:

Claims 36-43, filed with the letter of 11 May 1999.

This report has been drawn on the basis of the drawings,
sheets, 1-10, as originally filed.

sheets, NONE, filed with the demand.

and additional amendments:

NONE

Inventors: Thomas G. Wilson
Julia N. Heinrich

RECOMBINANT bHLH-PAS/JHR POLYPEPTIDE AND ITS USE
TO SCREEN POTENTIAL INSECTICIDES

5

BACKGROUND OF THE INVENTION

The present invention relates to a cloned "basic helix loop helix -PER-ARNT-AhR-SIM" (bHLH-PAS) protein that is a juvenile hormone receptor (JHR), bHLH-PAS/JHR. In particular, this invention is directed to a bHLH-PAS/JHR gene isolated from *Drosophila*, termed the methoprene-tolerant (*met*) gene (*Met*-JHR). The present invention also is directed to *in vitro* and *in vivo* methods for screening insecticides using recombinant bHLH-PAS/JHRs. The present invention is further directed to methods for isolating polynucleotides encoding bHLH-PAS/JHRs from various insect species.

Worldwide insect damage to food and fiber costs billions of dollars annually. Although chemical insecticides are still the primary means of insect control, the use of chemicals has several drawbacks including high cost of discovery, potential environmental damage, and negative public opinion. One promising group of insecticides consists of analogues of insect hormones, such as juvenile hormone. Since vertebrates do not make juvenile hormone (JH), insecticides targeted to the JH system are highly toxic to certain insects, and have shown an extraordinary degree of environmental safety.

Juvenile hormones comprise a family of hormones that are secreted by the corpus allatum, and that play a role in a variety of critical functions in insects, including development, reproduction, and morphological differentiation. Riddiford, "Hormone Action at the

molecules. A genomic polynucleotide comprising the Met gene is the St-H fragment in Figure 1. This fragment is 6.234 Kb, and its sequence is shown in Figure 2 (SEQ ID NO:1). Within this 6.234 Kb segment, there is a DNA

5 sequence of 3.011 Kb, which includes an open reading frame that is divided by one intron of 69 nucleotides (bases 1520 to 1588). This 3.011 Kb sequence is the genomic Met-JHR DNA sequence. Figure 3 (SEQ ID NO:2).

The Met-JHR open reading frame lacking the intron
10 codes for a protein of 716 amino acids and a having a molecular weight of about 78,720 daltons.

The nucleotide sequences of the genomic and cDNA Met-JHR differ, reflecting polymorphism. In Figure 3, SEQ ID NO:3 represents a Met-JHR cDNA sequence, which begins at
15 nucleotide 4 of the genomic sequence. There is one "polymorphic" difference between the genomic and cDNA nucleotide sequences that results in a change at the amino acid level. The nucleotide at position 1043 (genomic)/1039 (cDNA) may be C or T, which results in
20 different deduced amino acids, R and W, respectively.

In the sequence of the genomic DNA, there is one ambiguity that results in different deduced amino acids. Base number 875 in the genomic DNA is designated "R," which signifies that the nucleotide may be the purine C
25 or G. This results in two possible corresponding deduced amino acid sequences, G (Gly) or R (Arg) respectively. In the sequence of the cDNA, there is one ambiguity that results in a different deduced amino acids. Base number 526 in the genomic DNA is designated "M," which signifies
30 that the nucleotide may be the purine A or C. This results in two possible corresponding deduced amino acid sequences, T (Thr) or P (Pro) respectively.

As used herein, the term "juvenile hormone receptor" (JHR) is used to mean a polypeptide that is
35 involved in binding JHIII. As used herein, a polypeptide that is "involved in binding" JHIII includes a

AMENDED SHEET

transcript with the genomic nucleotide sequence. The probable transcription start site for this transcript begins 220 bp upstream from the start codon and the probably transcript ends 912 bp from the stop codon.

5 A comparison of the cDNA to the genomic sequence showed that the genomic ORF is 2.22 Kb and the cDNA ORF is 2.151 Kb. The difference between the two sequences is a 69 nucleotide intron, which corresponds to 23 codons, and does not change the open reading frame of the genomic
10 and cDNA. The presence of the intron provides evidence for the possibility of alternatively spliced variants of Met-JHR and hence multiple isoform proteins of Met-JHR.

The longest single open reading frame in the cDNA in Figure 3 (SEQ ID NO:3) comprises a single open reading
15 frame (ORF). The DNA sequence (CAAAATGGCA) (SEQ ID NO:13) surrounding this ATG of the ORF is in good agreement with a *Drosophila* translation start site consensus sequence. Cavener Nucl. Acid. Res. 15:1353 (1987).

20 The first genomic exon is from position 224 to position 1543 (1296 bases). This is followed by a 69 bp intron, and a second exon, which extends from position 1589 to 2443 (855 bases). The remainder of the Met-JHR gene is from 2443 to 3011 (568 bases). The total length
25 of the nucleotide sequence provided for the genomic DNA is 3011 nucleotides (SEQ ID NO:2), and that of the cDNA is 3282 nucleotides (SEQ ID NO:3).

Comparison of the Met-JHR ORF and with sequences deposited in the Genbank database showed three regions of
30 homology to members of a family of transcriptional activators known as the basic helix-loop-helix-Per-Arnt-Sim (bhlh-PAS) proteins. See Figure 6. Three vertebrate members of this family include the aromatic hydrocarbon receptor nuclear translocator (ARNT), muscle and brain
35 ARNT-like protein 1 (BMAL-1), and the aromatic hydrocarbon receptor (AHR). Three *Drosophila* family

members include ARNT (DARNT), Trachealess (Trh) and Single-minded (Sim).

The ARNT and AHR proteins are involved as heterodimeric partners in binding a variety of environmental toxicants, including dioxin, and subsequently activating a variety of genes important in the degradation of these chemicals, such as the cytochrome P450 genes. Figure 6 indicates that Met-JHR is neither DARNT nor AHR. However, Met-JHR shares considerable homology to human AHR in the ligand binding region of AHR, which is amino acids 200-400 of AHR. Rowlands et al. *Crit. Rev. Toxicol.* 27:109 (1997). Another feature apparent from visual inspection of the Met-JHR sequence is that Met-JHR, like human ARH (HARH), has a high concentration of serine and threonine residues at its carboxyl terminus. This is the motif of a S/P/T transactivation domain, as noted above. In ARH, this domain has been shown to be a functional TAD.

These features support the hypothesis that the mechanism of action of Met-JHR is similar to AHR, i.e., Met-JHR binds the JH ligand. In addition, the Met-JHR may heterodimerize to DARNT or a DARNT-like protein in order to bind a JH response element and mediate JH action. The bHLH domain has been shown to be involved in dimerization and DNA binding. Rowlands et al. *Critical Reviews in Toxicology*, 27: 109 (1997).

Met-JHR also contains the "LXXLL" (SEQ ID NO:14) motif which likens Met to steroid receptor co-activators. Although this motif is found in many proteins, it plays a significant role in proteins that interact with co-activators of steroid receptors. LXXLL (SEQ ID NO:14) also has been found in a bHLH-PAS protein that is a cofactor (ACTR) [Chen et al. *Cell* 90:569 (1997)] that is amplified in breast cancer-1 (AIBC). Anzick et al. *Science* 277:965 (1997). This bHLH-PAS protein (ACTR/AIBC) interacts with a steroid

and the DNA binding region of a second polypeptide, (2) DNA encoding a bHLH-PAS polypeptide and the activation domain of said second polypeptide, and (3) a reporter gene under the control of a minimal promoter driven by the response element for said second polypeptide;

(b) incubating a test compound with said host cell; and

(c) detecting the binding of the test compound with said bHLH-PAS polypeptide by monitoring expression of the reporter gene.

37. A method according to claim 32, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

38. A method according to claim 33, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

39. A method according to claim 34, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

40. A method according to claim 35, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

41. A method according to claim 36, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

10 | 42. An isolated polynucleotide which comprises the sequence of SEQ ID NO:6.

43. An isolated polynucleotide which comprises the sequence of SEQ ID NO:7.

09403936 010300

SEQUENCE LISTING

<110> Wilson, Thomas G.
Heinrich, Julia N.
American Cyanamid Company

<120> RECOMBINANT BHLH-PAS/JHR POLYPEPTIDE AND ITS USE TO
SCREEN POTENTIAL INSECTICIDES

<130> 082584/104

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AMENDED SHEET

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<211> 737

<212> PRT

<213> Met-JHR

<220>

<223> Xaa at position 218 may be Thr or Pro

<400> 4

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Asp Pro Ala Asn Gly Arg Glu Ala Arg Asn Leu Ala Glu Lys Gln Arg
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Arg Asp Lys Leu Asn Ala Ser Ile Gln Glu Leu Ala Thr Met Val Pro
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His Ala Ala Glu Ser Ser Arg Arg Leu Asp Lys Thr Ala Val Leu Arg
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Phe Ala Thr His Gly Leu Arg Leu Gln Tyr Val Phe Gly Lys Ser Ala
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Ser Arg Arg Arg Lys Lys Thr Gly Leu Lys Gly Thr Gly Met Ser Ala
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Ser Pro Val Gly Asp Leu Pro Asn Pro Ser Leu His Leu Thr Asp Thr
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Leu Met Gln Leu Leu Asp Cys Cys Phe Leu Thr Leu Thr Cys Ser Gly
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Gln Ile Val Leu Val Ser Thr Ser Val Glu Gln Leu Leu Gly His Cys
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Gln Ser Asp Leu Tyr Gly Gln Asn Leu Leu Gln Ile Thr His Pro Asp
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Asp Gln Asp Leu Leu Arg Gln Gln Leu Ile Pro Arg Asp Ile Glu Thr
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Leu Phe Tyr Gln His Gln His His Gln Gln Gln Gly His Asn Pro Gln
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Gln His Ser Thr Ser Thr Ser Ala Ser Xaa Ser Gly Ser Asp Leu Glu
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AMENDED SHEET

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 Pro Arg Arg Met Ala His Leu Ala Thr Ile Asp Asp Arg Leu Arg Met
 260 265 270
 Asp Arg Arg Cys Phe Thr Val Arg Leu Ala Arg Ala Ser Thr Arg Ala
 275 280 285
 Glu Ala Thr Arg His Tyr Glu Arg Val Lys Ile Asp Gly Cys Phe Arg
 290 295 300
 Arg Ser Asp Ser Ser Leu Thr Gly Gly Ala Ala Ala Asn Tyr Pro Ile
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 Val Ser Gln Leu Ile Arg Arg Ser Arg Asn Asn Asn Met Leu Ala Ala
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 Ala Ala Ala Val Ala Ala Glu Ala Ala Thr Val Pro Pro Gln His Asp
 340 345 350
 Ala Ile Ala Gln Ala Ala Leu His Gly Ile Ser Gly Asn Asp Ile Val
 355 360 365
 Leu Val Ala Met Ala Arg Val Leu Arg Glu Glu Arg Pro Pro Glu Glu
 370 375 380
 Thr Glu Gly Thr Val Gly Leu Thr Ile Tyr Arg Gln Pro Glu Pro Tyr
 385 390 395 400
 Gln Leu Glu Tyr His Thr Arg His Leu Ile Asp Gly Ser Ile Ile Asp
 405 410 415
 Cys Asp Gln Arg Ile Gly Leu Val Ala Gly Tyr Met Lys Asp Glu Val
 420 425 430
 Gly Ile Leu Thr Ser Ser Leu Thr Ala Tyr Asp Asn Ser Cys Thr Leu
 435 440 445
 His Ser Lys Gln Val Arg Asn Leu Ser Pro Phe Cys Phe Met His Leu
 450 455 460
 Asp Asp Val Arg Trp Val Ile Val Ala Leu Arg Gln Met Tyr Asp Cys
 465 470 475 480
 Asn Ser Asp Tyr Gly Glu Ser Cys Tyr Arg Leu Leu Ser Arg Asn Gly
 485 490 495
 Arg Phe Ile Tyr Leu His Thr Lys Gly Phe Leu Glu Val Asp Arg Gly
 500 505 510
 Ser Asn Lys Val His Ser Phe Leu Cys Val Asn Thr Leu Leu Asp Glu
 515 520 525
 Glu Ala Gly Arg Gln Lys Val Gln Glu Met Lys Glu Lys Phe Ser Thr
 530 535 540

AMENDED SHEET

Ile Ile Lys Ala Glu Met Pro Thr Gln Ser Ser Ser Pro Asp Leu Pro
545 550 555 560

Ala Ser Gln Ala Pro Gln Gln Leu Glu Arg Ile Val Leu Tyr Leu Ile
565 570 575

Glu Asn Leu Gln Lys Ser Val Asp Ser Ala Glu Thr Val Gly Gly Gln
580 585 590

Gly Met Glu Ser Leu Met Asp Asp Gly Tyr Ser Ser Pro Ala Asn Thr
595 600 605

Leu Thr Leu Glu Glu Leu Ala Pro Ser Pro Thr Pro Ala Leu Ala Leu
610 615 620

Val Pro Pro Ala Pro Ser Ser Val Lys Ser Ser Ile Ser Lys Ser Val
625 630 635 640

Ser Val Val Asn Val Thr Ala Ala Arg Lys Phe Gln Gln Glu His Gln
645 650 655

Lys Gln Arg Glu Arg Asp Arg Glu Gln Leu Lys Glu Arg Thr Asn Ser
660 665 670

Thr Gln Gly Val Ile Arg Gln Leu Ser Ser Cys Leu Ser Glu Ala Glu
675 680 685

Thr Ala Ser Cys Ile Leu Ser Pro Ala Ser Ser Leu Ser Ala Ser Glu
690 695 700

Ala Pro Asp Thr Pro Asp Pro His Ser Asn Thr Ser Pro Pro Pro Ser
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Leu His Thr Arg Pro Ser Val Leu His Arg Thr Leu Thr Ser Thr Leu
725 730 735

Arg

<210> 5
<211> 716
<212> PRT
<213> Met-JHR

<220>
<223> Xaa at position 103 may be Gly or Arg

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Ser Thr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser
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Asp Pro Ala Asn Gly Arg Glu Ala Arg Asn Leu Ala Glu Lys Gln Arg
35 40 45

Arg Asp Lys Leu Asn Ala Ser Ile Gln Glu Leu Ala Thr Met Val Pro
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Glu	Ala	Thr	Arg	His	Tyr	Glu	Arg	Val	Lys	Ile	Asp	Gly	Cys	Phe	Arg	290	295	300	
Arg	Ser	Asp	Ser	Ser	Leu	Thr	Gly	Gly	Ala	Ala	Ala	Asn	Tyr	Pro	Ile	305	310	315	320
Val	Ser	Gln	Leu	Ile	Arg	Arg	Ser	Arg	Asn	Asn	Asn	Met	Leu	Ala	Ala	325	330	335	
Ala	Ala	Ala	Val	Ala	Ala	Glu	Ala	Ala	Thr	Val	Pro	Pro	Gln	His	Asp	340	345	350	
Ala	Ile	Ala	Gln	Ala	Ala	Leu	His	Gly	Ile	Ser	Gly	Asn	Asp	Ile	Val	355	360	365	
Leu	Val	Ala	Met	Ala	Arg	Val	Leu	Arg	Glu	Glu	Arg	Pro	Pro	Glu	Glu	370	375	380	

AMENDED SHEET

Thr Glu Gly Thr Val Gly Leu Thr Ile Tyr Arg Gln Pro Glu Pro Tyr
 385 390 395 400
 Gln Leu Glu Tyr His Thr Arg His Leu Ile Asp Gly Ser Ile Ile Asp
 405 410 415
 Cys Asp Gln Arg Ile Gly Leu Val Ala Gly Tyr Met Lys Asp Glu Val
 420 425 430
 Arg Asn Leu Ser Pro Phe Cys Phe Met His Leu Asp Asp Val Arg Trp
 435 440 445
 Val Ile Val Ala Leu Arg Gln Met Tyr Asp Cys Asn Ser Asp Tyr Gly
 450 455 460
 Glu Ser Cys Tyr Arg Leu Leu Ser Arg Asn Gly Arg Phe Ile Tyr Leu
 465 470 475 480
 His Thr Lys Gly Phe Leu Glu Val Asp Arg Gly Ser Asn Lys Val His
 485 490 495
 Ser Phe Leu Cys Val Asn Thr Leu Leu Asp Glu Glu Ala Gly Arg Gln
 500 505 510
 Lys Val Gln Glu Met Lys Glu Lys Phe Ser Thr Ile Ile Lys Ala Glu
 515 520 525
 Met Pro Thr Gln Ser Ser Ser Pro Asp Leu Pro Ala Ser Gln Ala Pro
 530 535 540
 Gln Gln Leu Glu Arg Ile Val Leu Tyr Leu Ile Glu Asn Leu Gln Lys
 545 550 555 560
 Ser Val Asp Ser Ala Glu Thr Val Gly Gly Gln Gly Met Glu Ser Leu
 565 570 575
 Met Asp Asp Gly Tyr Ser Ser Pro Ala Asn Thr Leu Thr Leu Glu Glu
 580 585 590
 Leu Ala Pro Ser Pro Thr Pro Ala Leu Ala Leu Val Pro Pro Ala Pro
 595 600 605
 Ser Ser Val Lys Ser Ser Ile Ser Lys Ser Val Ser Val Val Asn Val
 610 615 620
 Thr Ala Ala Arg Lys Phe Gln Gln Glu His Gln Lys Gln Arg Glu Arg
 625 630 635 640
 Asp Arg Glu Gln Leu Lys Glu Arg Thr Asn Ser Thr Gln Gly Val Ile
 645 650 655
 Arg Gln Leu Ser Ser Cys Leu Ser Glu Ala Glu Thr Ala Ser Cys Ile
 660 665 670
 Leu Ser Pro Ala Ser Ser Leu Ser Ala Ser Glu Ala Pro Asp Thr Pro
 675 680 685
 Asp Pro His Ser Asn Thr Ser Pro Pro Pro Ser Leu His Thr Arg Pro
 690 695 700

AMENDED SHEET

Ser Val Leu His Arg Thr Leu Thr Ser Thr Leu Arg
705 710 715

<210> 6
<211> 250
<212> DNA
<213> D. melanogaster

<400> 6
atggcagcac cagagacggg caacacgggc tccacaggat ccgctggctc gacaggatcg 60
ggatcgggat cgggatcggg aagtgggagc tcctcagatc cagcgaatgg acgggaggcc 120
cgtaaccttg ccgaaaaaca gcgacgggat aagcttaatg ccagcatcca ggagctggct 180
accatggtac cacatgcagc cgaatcctcc cgtcgcctgg acaaaaccgc cgtccttaga 240
ttcgccaccc 250

<210> 7
<211> 232
<212> DNA
<213> D. erecta

<400> 7
cagcagacgc gggcaacacg ggcaccacag gatcagctgg gtccacagga tctgggatcgg 60
gaactgggac gtccgcagat ccagcgaatg gacgggaggc ccgcaatctt gccgagaaac 120
agcgacggga taagcttaat gccagcatcc aggagctggc taccatggta ccacatgtca 180
gccgaatcct cccgacgcct ggacaaaacc gccgtcctca gattcgccac cc 232

<210> 8
<211> 631
<212> PRT
<213> Drosophila

<400> 8
Met Asp Glu Ala Asn Ile Gln Asp Lys Glu Arg Phe Ala Ser Arg Glu
1 5 10 15
Asn His Cys Glu Ile Glu Arg Arg Arg Asn Lys Met Thr Ala Tyr
20 25 30
Ile Thr Glu Leu Ser Asp Met Val Pro Thr Cys Ser Ala Leu Ala Arg
35 40 45
Lys Pro Asp Lys Leu Thr Ile Leu Arg Met Ala Val Ala His Met Lys
50 55 60
Ala Leu Arg Gly Thr Gly Asn Thr Ser Ser Asp Gly Thr Tyr Lys Pro
65 70 75 80
Ser Phe Leu Thr Asp Gln Glu Leu Lys His Leu Ile Leu Glu Ala Ala
85 90 95
Asp Gly Phe Leu Phe Val Val Ser Cys Asp Ser Gly Arg Val Ile Tyr
100 105 110
Val Ser Asp Ser Val Thr Pro Val Leu Asn Tyr Thr Gln Ser Asp Trp
115 120 125
Tyr Gly Thr Ser Leu Tyr Glu His Ile His Pro Asp Asp Arg Glu Lys
130 135 140

AMENDED SHEET

Ile 145	Arg	Glu	Gln	Leu	Ser 150	Thr	Gln	Glu	Ser	Gln 155	Asn	Ala	Gly	Arg	Ile 160
Leu	Asp	Leu	Lys	Ser 165	Gly	Thr	Val	Lys	Lys 170	Glu	Gly	His	Gln	Ser	Ser 175
Met	Arg	Leu	Ser 180	Met	Gly	Ala	Arg	Arg	Gly 185	Phe	Ile	Cys	Met	Arg	Val 190
Gly	Asn	Val 195	Asn	Pro	Glu	Ser	Met 200	Val	Ser	Gly	His	Leu 205	Asn	Arg	Leu
Lys	Gln	Arg	Asn	Ser	Leu	Gly 215	Pro	Ser	Arg	Asp	Gly 220	Thr	Asn	Tyr	Ala
Val 225	Val	His	Cys	Thr	Gly 230	Tyr	Ile	Lys	Asn	Trp 235	Pro	Pro	Thr	Asp	Met 240
Phe	Pro	Asn	Met	His 245	Met	Glu	Arg	Asp	Val 250	Asp	Asp	Met	Ser	Ser	His 255
Cys	Cys	Leu	Val 260	Ala	Ile	Gly	Arg	Leu 265	Gln	Val	Thr	Ser	Thr 270	Ala	Ala
Asn	Asp	Met 275	Ser	Gly	Ser	Asn	Asn 280	Gln	Ser	Glu	Phe	Ile 285	Thr	Arg	His
Ala	Met 290	Asp	Gly	Lys	Phe	Thr 295	Phe	Val	Asp	Gln	Arg 300	Val	Leu	Asn	Ile
Leu 305	Gly	Tyr	Thr	Pro	Thr 310	Glu	Leu	Leu	Gly	Lys 315	Ile	Cys	Tyr	Asp	Phe 320
Phe	His	Pro	Glu	Asp 325	Gln	Ser	His	Met	Lys 330	Glu	Ser	Phe	Asp	Gln 335	Val
Leu	Lys	Gln	Lys 340	Gly	Gln	Met	Phe	Ser 345	Leu	Leu	Tyr	Arg	Ala 350	Arg	Ala
Lys	Asn	Ser 355	Glu	Tyr	Tyr	Val	Trp 360	Leu	Arg	Thr	Gln	Ala 365	Tyr	Ala	Phe
Leu 370	Asn	Pro	Tyr	Thr	Asp	Glu 375	Val	Glu	Tyr	Ile	Val 380	Cys	Thr	Asn	Ser
Ser 385	Gly	Lys	Thr	Met	His 390	Gly	Ala	Pro	Leu	Asp 395	Ala	Ala	Ala	Ala	His 400
Thr	Pro	Glu	Gln	Val 405	Gln	Gln	Gln	Gln	Gln 410	Gln	Gln	Gln	Gln	Glu	His 415
Val	Tyr	Val	Gln 420	Ala	Ala	Pro	Gly	Val 425	Asp	Tyr	Ala	Arg	Arg 430	Glu	Leu
Thr	Pro	Val 435	Gly	Ser	Ala	Thr	Asn 440	Asp	Gly	Met	Tyr	Gln 445	Thr	His	Met
Leu 450	Ala	Met	Gln	Ala	Pro	Thr 455	Pro	Gln	Gln	Gln	Gln 460	Gln	Gln	Gln	Gln

Arg Pro Gly Ser Ala Gln Thr Thr Pro Val Gly Tyr Thr Tyr Asp Thr
 465 470 475 480
 Thr His Ser Pro Tyr Ser Ala Gly Gly Thr Ser Pro Leu Ala Lys Ile
 485 490 495
 Pro Lys Ser Gly Thr Ser Pro Thr Pro Val Ala Pro Asn Ser Trp Ala
 500 505 510
 Ala Leu Arg Pro Gln Gln Gln Gln Gln Gln Gln Gln Pro Val Thr Glu
 515 520 525
 Gly Tyr Gln Tyr Gln Gln Thr Ser Pro Ala Arg Ser Pro Ser Gly Pro
 530 535 540
 Thr Tyr Thr Gln Leu Ser Ala Gly Asn Gly Asn Arg Gln Gln Ala Gln
 545 550 555 560
 Pro Gly Ala Tyr Gln Ala Gly Pro Pro Pro Pro Pro Asn Ala Pro Gly
 565 570 575
 Met Trp Asp Trp Gln Gln Ala Gly Gly His Pro His Pro Pro His Pro
 580 585 590
 Thr Ala His Pro His His Pro His Ala His Pro Gly Gly Pro Ala Gly
 595 600 605
 Ala Gly Gln Pro Gln Gly Gln Gly Val Leu Arg Tyr Ala Ala Asp Val
 610 615 620
 Gly Ser His Ala Asp His Val
 625 630

<210> 9
 <211> 789
 <212> PRT
 <213> human

<400> 9

Met Ala Ala Thr Thr Ala Asn Pro Glu Met Thr Ser Asp Val Pro Ser
 1 5 10 15
 Leu Gly Pro Ala Ile Ala Ser Gly Asn Ser Gly Pro Gly Ile Gln Gly
 20 25 30
 Gly Gly Ala Ile Val Gln Arg Ala Ile Lys Arg Arg Pro Gly Leu Asp
 35 40 45
 Phe Asp Asp Asp Gly Glu Gly Asn Ser Lys Phe Leu Arg Cys Asp Asp
 50 55 60
 Asp Gln Met Ser Asn Asp Lys Glu Arg Phe Ala Arg Ser Asp Asp Glu
 65 70 75 80
 Gln Ser Ser Ala Asp Lys Glu Arg Leu Ala Arg Glu Asn His Ser Glu
 85 90 95
 Ile Glu Arg Arg Arg Arg Asn Lys Met Thr Ala Tyr Ile Thr Glu Leu
 100 105 110

AMENDED SHEET

Ser Asp Met Val Pro Thr Cys Ser Ala Leu Ala Arg Lys Pro Asp Lys
 115 120 125
 Leu Thr Ile Leu Arg Met Ala Val Ser His Met Lys Ser Leu Arg Gly
 130 135 140
 Thr Gly Asn Thr Ser Thr Asp Gly Ser Tyr Lys Pro Ser Phe Leu Thr
 145 150 155 160
 Asp Gln Glu Leu Lys His Leu Ile Leu Glu Ala Ala Asp Gly Phe Leu
 165 170 175
 Phe Ile Val Ser Cys Glu Thr Gly Arg Val Val Tyr Val Ser Asp Ser
 180 185 190
 Val Thr Pro Val Leu Asn Gln Pro Gln Ser Glu Trp Phe Gly Ser Thr
 195 200 205
 Leu Tyr Asp Gln Val His Pro Asp Asp Val Asp Lys Leu Arg Glu Gln
 210 215 220
 Leu Ser Thr Ser Glu Asn Ala Leu Thr Gly Arg Ile Leu Asp Leu Lys
 225 230 235 240
 Thr Gly Thr Val Lys Lys Glu Gly Gln Gln Ser Ser Met Arg Met Cys
 245 250 255
 Met Gly Ser Arg Arg Ser Phe Ile Cys Arg Met Arg Cys Gly Ser Ser
 260 265 270
 Ser Val Asp Pro Val Ser Val Asn Arg Leu Ser Phe Val Arg Asn Arg
 275 280 285
 Cys Arg Asn Gly Leu Gly Ser Val Lys Asp Gly Glu Pro His Phe Val
 290 295 300
 Val Val His Cys Thr Gly Tyr Ile Lys Ala Trp Pro Pro Ala Gly Val
 305 310 315 320
 Ser Leu Pro Asp Asp Asp Pro Glu Ala Gly Gln Gly Ser Lys Phe Cys
 325 330 335
 Leu Val Ala Ile Gly Arg Leu Gln Val Thr Ser Ser Pro Asn Cys Thr
 340 345 350
 Asp Met Ser Asn Val Cys Gln Pro Thr Glu Phe Ile Ser Arg His Asn
 355 360 365
 Ile Glu Gly Ile Phe Thr Phe Val Asp His Arg Cys Val Ala Thr Val
 370 375 380
 Gly Tyr Gln Pro Gln Glu Leu Leu Gly Lys Asn Ile Val Glu Phe Cys
 385 390 395 400
 His Pro Glu Asp Gln Gln Leu Leu Arg Asp Ser Phe Gln Gln Val Val
 405 410 415
 Lys Leu Lys Gly Gln Val Leu Ser Val Met Phe Arg Phe Arg Ser Lys
 420 425 430

AMENDED SHEET

Asn	Gln	Glu	Trp	Leu	Trp	Met	Arg	Thr	Ser	Ser	Phe	Thr	Phe	Gln	Asn	435	440	445
Pro	Tyr	Ser	Asp	Glu	Ile	Glu	Tyr	Ile	Ile	Cys	Thr	Asn	Thr	Asn	Val	450	455	460
Lys	Asn	Ser	Ser	Gln	Glu	Pro	Arg	Pro	Thr	Leu	Ser	Asn	Thr	Ile	Gln	465	470	475
Arg	Pro	Gln	Leu	Gly	Pro	Thr	Ala	Asn	Leu	Pro	Leu	Glu	Met	Gly	Ser	485	490	495
Gly	Gln	Leu	Ala	Pro	Arg	Gln	Gln	Gln	Gln	Gln	Thr	Glu	Leu	Asp	Met	500	505	510
Val	Pro	Gly	Arg	Asp	Gly	Leu	Ala	Ser	Tyr	Asn	His	Ser	Gln	Val	Val	515	520	525
Gln	Pro	Val	Thr	Thr	Thr	Gly	Pro	Glu	His	Ser	Lys	Pro	Leu	Glu	Lys	530	535	540
Ser	Asp	Gly	Leu	Phe	Ala	Gln	Asp	Arg	Asp	Pro	Arg	Phe	Ser	Glu	Ile	545	550	555
Tyr	His	Asn	Ile	Asn	Ala	Asp	Gln	Ser	Lys	Gly	Ile	Ser	Ser	Ser	Thr	565	570	575
Val	Pro	Ala	Thr	Gln	Gln	Leu	Phe	Ser	Gln	Gly	Asn	Thr	Phe	Pro	Pro	580	585	590
Thr	Pro	Arg	Pro	Ala	Glu	Asn	Phe	Arg	Asn	Ser	Gly	Leu	Ala	Pro	Pro	595	600	605
Val	Thr	Ile	Val	Gln	Pro	Ser	Ala	Ser	Ala	Gly	Gln	Met	Leu	Ala	Gln	610	615	620
Ile	Ser	Arg	His	Ser	Asn	Pro	Thr	Gln	Gly	Ala	Thr	Pro	Thr	Trp	Thr	625	630	635
Pro	Thr	Thr	Arg	Ser	Gly	Phe	Ser	Ala	Gln	Gln	Val	Ala	Thr	Gln	Ala	645	650	655
Thr	Ala	Lys	Thr	Arg	Thr	Ser	Gln	Phe	Gly	Val	Gly	Ser	Phe	Gln	Thr	660	665	670
Pro	Ser	Ser	Phe	Ser	Ser	Met	Ser	Leu	Pro	Gly	Ala	Pro	Thr	Ala	Ser	675	680	685
Pro	Gly	Ala	Ala	Ala	Tyr	Pro	Ser	Leu	Thr	Asn	Arg	Gly	Ser	Asn	Phe	690	695	700
Ala	Pro	Glu	Thr	Gly	Gln	Thr	Ala	Gly	Gln	Phe	Gln	Thr	Arg	Thr	Ala	705	710	715
Glu	Gly	Val	Gly	Val	Trp	Pro	Gln	Trp	Gln	Gly	Gln	Gln	Pro	His	His	725	730	735
Arg	Ser	Ser	Ser	Ser	Glu	Gln	His	Val	Gln	Gln	Pro	Pro	Ala	Gln	Gln	740	745	750

AMENDED SHEET

Pro Gly Gln Pro Glu Val Phe Gln Glu Met Leu Ser Met Leu Gly Asp
 755 760 765
 Gln Ser Asn Ser Tyr Asn Asn Glu Glu Phe Pro Asp Leu Thr Met Phe
 770 775 780
 Pro Pro Phe Ser Glu
 785

<210> 10
 <211> 626
 <212> PRT
 <213> brain and muscle ARNT-like protein a

<400> 10
 Met Ala Asp Gln Arg Met Asp Ile Ser Ser Thr Ile Ser Asp Phe Met
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 Ser Pro Gly Pro Thr Asp Leu Leu Ser Ser Ser Leu Gly Thr Ser Gly
 20 25 30
 Val Asp Cys Asn Arg Lys Arg Lys Gly Ser Ser Thr Asp Tyr Gln Glu
 35 40 45
 Ser Met Asp Thr Asp Lys Asp Asp Pro His Gly Arg Leu Glu Tyr Thr
 50 55 60
 Glu His Gln Gly Arg Ile Lys Asn Ala Arg Glu Ala His Ser Gln Ile
 65 70 75 80
 Glu Lys Arg Arg Arg Asp Lys Met Asn Ser Phe Ile Asp Glu Leu Ala
 85 90 95
 Ser Leu Val Pro Thr Cys Asn Ala Met Ser Arg Lys Leu Asp Lys Leu
 100 105 110
 Thr Val Leu Arg Met Ala Val Gln His Met Arg Thr Leu Arg Gly Ala
 115 120 125
 Thr Asn Pro Tyr Thr Glu Ala Asn Tyr Lys Pro Thr Phe Leu Ser Asp
 130 135 140
 Asp Glu Leu Lys His Leu Ile Leu Arg Ala Ala Asp Gly Phe Leu Phe
 145 150 155 160
 Val Val Gly Cys Asp Arg Gly Lys Ile Leu Phe Val Ser Glu Ser Val
 165 170 175
 Phe Lys Ile Leu Asn Tyr Ser Gln Asn Asp Leu Ile Gly Gln Ser Leu
 180 185 190
 Phe Asp Tyr Leu His Pro Lys Asp Ile Ala Lys Val Lys Glu Gln Leu
 195 200 205
 Ser Ser Ser Asp Thr Ala Pro Arg Glu Arg Leu Ile Asp Ala Lys Thr
 210 215 220
 Gly Leu Pro Val Lys Thr Asp Ile Thr Pro Gly Pro Ser Arg Leu Cys
 225 230 235 240

AMENDED SHEET

Ser Gly Ala Arg Arg Ser Phe Phe Cys Arg Met Lys Cys Asn Arg Pro
 245 250 255
 Ser Val Lys Val Glu Asp Lys Asp Phe Pro Ser Thr Cys Ser Lys Lys
 260 265 270
 Lys Ala Asp Arg Lys Ser Phe Cys Thr Ile His Ser Thr Gly Tyr Leu
 275 280 285
 Lys Ser Trp Pro Pro Thr Lys Met Gly Leu Asp Glu Asp Asn Glu Pro
 290 295 300
 Asp Asn Glu Gly Cys Asn Leu Ser Cys Leu Val Ala Ile Gly Arg Leu
 305 310 315 320
 His Ser His Val Val Pro Gln Pro Val Asn Gly Glu Ile Arg Val Lys
 325 330 335
 Ser Met Glu Tyr Val Ser Arg His Ala Ile Asp Gly Lys Phe Val Phe
 340 345 350
 Val Asp Gln Arg Ala Thr Ala Ile Leu Ala Tyr Leu Pro Gln Glu Leu
 355 360 365
 Leu Gly Thr Ser Cys Tyr Glu Tyr Phe His Gln Asp Asp Ile Gly His
 370 375 380
 Leu Ala Glu Cys His Arg Gln Val Leu Gln Thr Arg Glu Lys Ile Thr
 385 390 395 400
 Thr Asn Cys Tyr Lys Phe Lys Ile Lys Asp Gly Ser Phe Ile Thr Leu
 405 410 415
 Arg Ser Arg Trp Phe Ser Phe Met Asn Pro Trp Thr Lys Glu Val Glu
 420 425 430
 Tyr Ile Val Ser Thr Asn Thr Val Val Leu Ala Asn Val Leu Glu Gly
 435 440 445
 Gly Asp Pro Thr Phe Pro Gln Leu Thr Ala Ser Pro His Ser Met Asp
 450 455 460
 Ser Met Leu Pro Ser Gly Glu Gly Gly Pro Lys Arg Thr His Pro Thr
 465 470 475 480
 Val Pro Gly Ile Pro Gly Gly Thr Arg Ala Gly Ala Gly Lys Ile Gly
 485 490 495
 Arg Met Ile Ala Glu Glu Ile Met Glu Ile His Arg Ile Arg Gly Ser
 500 505 510
 Ser Pro Ser Ser Cys Gly Ser Ser Pro Leu Asn Ile Thr Ser Thr Pro
 515 520 525
 Pro Pro Asp Ala Ser Ser Pro Gly Gly Lys Lys Ile Leu Asn Gly Gly
 530 535 540
 Thr Pro Asp Ile Pro Ser Ser Gly Leu Leu Ser Gly Gln Ala Gln Glu
 545 550 555 560

AMENDED SHEET

Asn Pro Gly Tyr Pro Tyr Ser Asp Ser Ser Ser Ile Leu Gly Glu Asn
565 570 575

Pro His Ile Gly Ile Asp Met Ile Asp Asn Asp Gln Gly Ser Ser Ser
580 585 590

Pro Ser Asn Asp Glu Ala Ala Met Ala Val Ile Met Ser Leu Leu Glu
595 600 605

Ala Asp Ala Gly Leu Gly Gly Pro Val Asp Phe Ser Asp Leu Pro Trp
610 615 620

Pro Leu
625

<210> 11
<211> 716
<212> PRT
<213> Met-JHR

<400> 11

Met Ala Ala Pro Glu Thr Gly Asn Thr Gly Ser Thr Gly Ser Ala Gly
1 5 10 15

Ser Thr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser
20 25 30

Asp Pro Ala Asn Gly Arg Glu Ala Arg Asn Leu Ala Glu Lys Gln Arg
35 40 45

Arg Asp Lys Leu Asn Ala Ser Ile Gln Glu Leu Ala Thr Met Val Pro
50 55 60

His Ala Ala Glu Ser Ser Arg Arg Leu Asp Lys Thr Ala Val Leu Arg
65 70 75 80

Phe Ala Thr His Gly Leu Arg Leu Gln Tyr Val Phe Gly Lys Ser Ala
85 90 95

Ser Arg Arg Arg Lys Lys Pro Gly Leu Lys Gly Thr Gly Met Ser Ala
100 105 110

Ser Pro Val Gly Asp Leu Pro Asn Pro Ser Leu His Leu Thr Asp Thr
115 120 125

Leu Met Gln Leu Leu Asp Cys Cys Phe Leu Thr Leu Thr Cys Ser Gly
130 135 140

Gln Ile Val Leu Val Ser Thr Ser Val Glu Gln Leu Leu Gly His Cys
145 150 155 160

Gln Ser Asp Leu Tyr Gly Gln Asn Leu Leu Gln Ile Thr His Pro Asp
165 170 175

Asp Gln Asp Leu Leu Arg Gln Gln Leu Ile Pro Arg Asp Ile Glu Thr
180 185 190

Leu Phe Tyr Gln His Gln His His Gln Gln Gln Gly His Asn Pro Gln
195 200 205

AMENDED SHEET

Gln His Ser Thr Ser Thr Ser Ala Ser Ala Ser Gly Ser Asp Leu Glu
 210 215 220

Glu Glu Glu Met Glu Thr Glu Glu His Arg Leu Gly Arg Gln Gln Gly
 225 230 235 240

Glu Ala Asp Asp Asp Glu Asp His Pro Tyr Asn Arg Arg Thr Pro Ser
 245 250 255

Pro Arg Arg Met Ala His Leu Ala Thr Ile Asp Asp Arg Leu Arg Met
 260 265 270

Asp Trp Arg Cys Phe Thr Val Arg Leu Ala Arg Ala Ser Thr Arg Ala
 275 280 285

Glu Ala Thr Arg His Tyr Glu Arg Val Lys Ile Asp Gly Cys Phe Arg
 290 295 300

Arg Ser Asp Ser Ser Leu Thr Gly Gly Ala Ala Ala Asn Tyr Pro Ile
 305 310 315 320

Val Ser Gln Leu Ile Arg Arg Ser Arg Asn Asn Asn Met Leu Ala Ala
 325 330 335

Ala Ala Ala Val Ala Ala Glu Ala Ala Thr Val Pro Pro Gln His Asp
 340 345 350

Ala Ile Ala Gln Ala Ala Leu His Gly Ile Ser Gly Asn Asp Ile Val
 355 360 365

Leu Val Ala Met Ala Arg Val Leu Arg Glu Glu Arg Pro Pro Glu Glu
 370 375 380

Thr Glu Gly Thr Val Gly Leu Thr Ile Tyr Arg Gln Pro Glu Pro Tyr
 385 390 395 400

Gln Leu Glu Tyr His Thr Arg His Leu Ile Asp Gly Ser Ile Ile Asp
 405 410 415

Cys Asp Gln Arg Ile Gly Leu Val Ala Gly Tyr Met Lys Asp Glu Val
 420 425 430

Arg Asn Leu Ser Pro Phe Cys Phe Met His Leu Asp Asp Val Arg Trp
 435 440 445

Val Ile Val Ala Leu Arg Gln Met Tyr Asp Cys Asn Ser Asp Tyr Gly
 450 455 460

Glu Ser Cys Tyr Arg Leu Leu Ser Arg Asn Gly Arg Phe Ile Tyr Leu
 465 470 475 480

His Thr Lys Gly Phe Leu Glu Val Asp Arg Gly Ser Asn Lys Val His
 485 490 495

Ser Phe Leu Cys Val Asn Thr Leu Leu Asp Glu Glu Ala Gly Arg Gln
 500 505 510

Lys Val Gln Glu Met Lys Glu Lys Phe Ser Thr Ile Ile Lys Ala Glu
 515 520 525

AMENDED SHEET

Met Pro Thr Gln Ser Ser Ser Pro Asp Leu Pro Ala Ser Gln Ala Pro
530 535 540

Gln Gln Leu Glu Arg Ile Val Leu Tyr Leu Ile Glu Asn Leu Gln Lys
545 550 555 560

Ser Val Asp Ser Ala Glu Thr Val Gly Gly Gln Gly Met Glu Ser Leu
565 570 575

Met Asp Asp Gly Tyr Ser Ser Pro Ala Asn Thr Leu Thr Leu Glu Glu
580 585 590

Leu Ala Pro Ser Pro Thr Pro Ala Leu Ala Leu Val Pro Pro Ala Pro
595 600 605

Ser Ser Val Lys Ser Ser Ile Ser Lys Ser Val Ser Val Val Asn Val
610 615 620

Thr Ala Ala Arg Lys Phe Gln Gln Glu His Gln Lys Gln Arg Glu Arg
625 630 635 640

Asp Arg Glu Gln Leu Lys Glu Arg Thr Asn Ser Thr Gln Gly Val Ile
645 650 655

Arg Gln Leu Ser Ser Cys Leu Ser Glu Ala Glu Thr Ala Ser Cys Ile
660 665 670

Leu Ser Pro Ala Ser Ser Leu Ser Ala Ser Glu Ala Pro Asp Thr Pro
675 680 685

Asp Pro His Ser Asn Thr Ser Pro Pro Pro Ser Leu His Thr Arg Pro
690 695 700

Ser Val Leu His Arg Thr Leu Thr Ser Thr Leu Arg
705 710 715

<210> 12
<211> 808
<212> PRT
<213> human

<400> 12

Met Asn Ser Ser Ser Ala Asn Ile Thr Tyr Ala Ser Arg Lys Arg Arg
1 5 10 15

Lys Pro Val Gln Lys Thr Val Lys Pro Ile Pro Ala Glu Gly Ile Lys
20 25 30

Ser Asn Pro Ser Lys Arg His Arg Asp Arg Leu Asn Thr Glu Leu Asp
35 40 45

Arg Leu Ala Ser Leu Leu Pro Phe Pro Gln Asp Val Ile Asn Lys Leu
50 55 60

Asp Lys Leu Ser Val Leu Arg Leu Ser Val Ser Tyr Leu Arg Ala Lys
65 70 75 80

Ser Phe Phe Asp Val Ala Leu Lys Ser Ser Pro Thr Glu Arg Asn Gly
85 90 95

Gly	Gln	Asp	Asn	Cys	Arg	Ala	Ala	Asn	Phe	Arg	Glu	Gly	Leu	Asn	Leu		
			100					105						110			
Gln	Glu	Gly	Glu	Phe	Leu	Leu	Gln	Ala	Leu	Asn	Gly	Phe	Val	Leu	Val		
		115					120					125					
Val	Thr	Thr	Asp	Ala	Leu	Val	Phe	Tyr	Ala	Ser	Ser	Thr	Ile	Gln	Asp		
	130					135					140						
Tyr	Leu	Gly	Phe	Gln	Gln	Ser	Asp	Val	Ile	His	Gln	Ser	Val	Tyr	Glu		
145					150					155					160		
Leu	Ile	His	Thr	Glu	Asp	Arg	Ala	Glu	Phe	Gln	Arg	Gln	Leu	His	Trp		
				165					170					175			
Ala	Leu	Asn	Pro	Ser	Gln	Cys	Thr	Glu	Ser	Gly	Gln	Gly	Ile	Glu	Glu		
			180					185						190			
Ala	Thr	Gly	Leu	Pro	Gln	Thr	Val	Val	Cys	Tyr	Asn	Pro	Asp	Gln	Ile		
		195					200					205					
Pro	Pro	Glu	Asn	Ser	Pro	Leu	Met	Glu	Arg	Cys	Phe	Ile	Cys	Arg	Leu		
	210					215					220						
Arg	Cys	Leu	Leu	Asp	Asn	Ser	Ser	Gly	Phe	Leu	Ala	Met	Asn	Phe	Gln		
225					230					235					240		
Gly	Lys	Leu	Lys	Tyr	Leu	His	Gly	Gln	Lys	Lys	Lys	Gly	Lys	Asp	Gly		
				245					250					255			
Ser	Ile	Leu	Pro	Pro	Gln	Leu	Ala	Leu	Phe	Ala	Ile	Ala	Thr	Pro	Leu		
			260					265					270				
Gln	Pro	Pro	Ser	Ile	Leu	Glu	Ile	Arg	Thr	Lys	Asn	Phe	Ile	Phe	Arg		
		275					280					285					
Thr	Lys	His	Lys	Leu	Asp	Phe	Thr	Pro	Ile	Gly	Cys	Asp	Ala	Lys	Gly		
	290					295					300						
Arg	Ile	Val	Leu	Gly	Tyr	Thr	Glu	Ala	Glu	Leu	Cys	Thr	Arg	Gly	Ser		
305					310					315					320		
Gly	Tyr	Gln	Phe	Ile	His	Ala	Ala	Asp	Met	Leu	Tyr	Cys	Ala	Glu	Ser		
				325					330					335			
His	Ile	Arg	Met	Ile	Lys	Thr	Gly	Glu	Ser	Gly	Met	Ile	Val	Phe	Arg		
			340					345					350				
Leu	Leu	Thr	Lys	Asn	Asn	Arg	Trp	Thr	Trp	Val	Gln	Ser	Asn	Ala	Arg		
		355					360					365					
Leu	Leu	Tyr	Lys	Asn	Gly	Arg	Pro	Asp	Tyr	Ile	Ile	Val	Thr	Gln	Arg		
	370					375					380						
Pro	Leu	Thr	Asp	Glu	Glu	Gly	Thr	Glu	His	Leu	Arg	Lys	Arg	Asn	Thr		
385					390					395					400		
Lys	Leu	Pro	Phe	Met	Phe	Thr	Thr	Gly	Glu	Ala	Val	Leu	Tyr	Glu	Ala		
				405					410					415			

AMENDED SHEET

Thr Asn Pro Phe Pro Ala Ile Met Asp Pro Leu Pro Leu Arg Thr Lys
 420 425 430
 Asn Gly Thr Ser Gly Lys Asp Ser Ala Thr Thr Ser Thr Leu Ser Lys
 435 440 445
 Asp Ser Leu Asn Pro Ser Ser Leu Leu Ala Ala Met Met Gln Gln Asp
 450 455 460
 Glu Ser Ile Tyr Leu Tyr Pro Ala Ser Ser Thr Ser Ser Thr Ala Pro
 465 470 475 480
 Phe Glu Asn Asn Phe Phe Asn Glu Ser Met Asn Glu Cys Arg Asn Trp
 485 490 495
 Gln Asp Asn Thr Ala Pro Met Gly Asn Asp Thr Ile Leu Lys His Glu
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 Gln Ile Asp Gln Pro Gln Asp Val Asn Ser Phe Ala Gly Gly His Pro
 515 520 525
 Gly Leu Phe Gln Asp Ser Lys Asn Ser Asp Leu Tyr Ser Ile Met Lys
 530 535 540
 Asn Leu Gly Ile Asp Phe Glu Asp Ile Arg His Met Gln Asn Glu Lys
 545 550 555 560
 Phe Phe Arg Asn Asp Phe Ser Gly Glu Val Asp Phe Arg Asp Ile Asp
 565 570 575
 Leu Thr Asp Glu Ile Leu Thr Tyr Val Gln Asp Ser Leu Ser Lys Ser
 580 585 590
 Pro Phe Ile Pro Ser Asp Tyr Gln Gln Gln Gln Ser Leu Ala Leu Asn
 595 600 605
 Ser Ser Cys Met Val Gln Glu His Leu His Leu Glu Gln Gln Gln Gln
 610 615 620
 His His Gln Lys Gln Val Val Val Glu Pro Gln Gln Gln Leu Cys Gln
 625 630 635 640
 Lys Met Lys His Met Gln Val Asn Gly Met Phe Glu Asn Trp Asn Ser
 645 650 655
 Asn Gln Phe Val Pro Phe Asn Cys Pro Gln Gln Asp Pro Gln Gln Tyr
 660 665 670
 Asn Val Phe Thr Asp Leu His Gly Ile Ser Gln Glu Phe Pro Tyr Lys
 675 680 685
 Ser Glu Met Asp Ser Met Pro Tyr Thr Gln Asn Phe Ile Ser Cys Asn
 690 695 700
 Gln Pro Val Leu Pro Gln His Ser Lys Cys Thr Glu Leu Asp Tyr Pro
 705 710 715 720
 Met Gly Ser Phe Glu Pro Ser Pro Tyr Pro Thr Thr Ser Ser Leu Glu
 725 730 735

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Asp Phe Val Thr Cys Leu Gln Leu Pro Glu Asn Gln Lys His Gly Leu
740 745 750

Asn Pro Gln Ser Ala Ile Ile Thr Pro Gln Thr Cys Tyr Ala Gly Ala
755 760 765

Val Ser Met Tyr Gln Cys Gln Pro Glu Pro Gln His Thr His Val Gly
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Gln Met Gln Tyr Asn Pro Val Leu Pro Gly Gln Gln Ala Phe Leu Asn
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Lys Phe Gln Asn Gly Val Phe Lys
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<211> 10

<212> DNA

<213> Met-JHR cDNA

<400> 13

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10

<210> 14

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<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: motif that
interacts with co-activators of steroid receptors

<220>

<223> Xaas may be any amino acid

<400> 14

Leu Xaa Xaa Leu Leu

1

5

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and the DNA binding region of a second polypeptide, (2) DNA encoding a bHLH-PAS polypeptide and the activation domain of said second polypeptide, and (3) a reporter gene under the control of a minimal promoter driven by the response element for said second polypeptide;

(b) incubating a test compound with said host cell; and

(c) detecting the binding of the test compound with said bHLH-PAS polypeptide by monitoring expression of the reporter gene.

37. A method according to claim 32, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

38. A method according to claim 33, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

39. A method according to claim 34, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

40. A method according to claim 35, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

41. A method according to claim 36, wherein said host cell is selected from the group of an insect cell, a yeast cell, and a mammalian cell.

42. An isolated polynucleotide which comprises the sequence of SEQ ID NO:6.

43. An isolated polynucleotide which comprises the sequence of SEQ ID NO:7.

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